UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Robert Taylor, Product Manager #25
Registration Division (TS-767)

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SUBJECT: Paraquat: Comments from Chevron Chemical Company on (HED/TOX) Evaluations, in 1980, of Four Lung Toxicity Studies with Rats. Dated May 6, 1981. EPA Accession No. 245700

TOX Chem. No. 634

Summary:

Toxicology Branch (HED) appreciates and accepts Chevron's comments regarding studies C, D and E (EPA Accession Nos. 241187, 241189 and 243856, respectively). Studies A and B (EPA Accession Nos. 241188 and 241818, respectively), although evaluated separately, have always been considered together in matters concerning inhalation toxicity of paraquat. We regret that we are unable to upgrade the classification of studies A and B. These studies are classified as supplementary because, considered individually or together, they are incomplete as subchronic inhalation studies.

Detailed Considerations:

The current submission (EPA Accession No. 245700) from Chevron Chemical Company (Chevron) represents a reply to two letters from Mr. Robert J. Taylor (Product Manager #25, EPA/RD), dated 4/1/80 and 9/5/80. These letters were concerned with the evaluations by Toxicology Branch of the following studies:

A. Three-week inhalation study (ICI 254/7449; CTL/C/729 dated 6/8/79; rat); EPA Accesssion No. 241188. Toxicology Branch classified this study as Core-Supplementary for the following reasons: 1) gross and histopathological examinations were restricted only to nasal passages, pharynx, larynx, trachea and lungs; 2) organs were not weighed; and 3) hematology and clinical chemistry analyses were not done.

B. Three-week inhalation study in rats exposed to an aerosol of prarquat: repeat study (ICI 279/79476; CTL/C/810 dated 12/5/79); EPA Accession No. 241818. Toxicology Branch classified this study as Core-Supplementary for the following reasons: 1) histopathology of tissues, including lung, was not performed at terminal kill; 2) organs were never weighed; and 3) hematology and clinical chemistry analyses were never done.

C. Paraquat concentrations in rat lungs following exposure to paraquat aerosols (ICI 254/7949; CTL/P/460; dated 8/17/79); EPA Accession No. 241187. This report is based on data obtained in the three-week inhalation study, CTL/C/729 (see A above). This report is concerned with levels of paraquat in rats lungs after 5 and 15 inhalation exposures, and after 1, 2, and 3 days of the recovery period. Toxicology Branch classified this study as Core-Minimum data in the category of SPECIAL TESTING (163.85-1).

D. Intrabronchial instillation of paraquat in rats: lung morphology and retention study (CTL/R/563; no date); EPA Accession No.241189. Toxicology Branch classified this study as Core-Minimum data in the category of SPECIAL TESTING (163.85-1).

Chevron listed also the following study in the current submission:

E. Assessment of accumulation of paraquat in the lung: 3-week inhalation study in rats (CTL/C/965; ICI 301/8037; dated 8/22/80); EPA Accession No. 243856. Toxicology Branch classified this study as Core-Supplementary (as an inhalation study) because the following parameters were never tested: gross necropsy, histopathology, hematology, clinical biochemistry, food intake, body and organ weights (other than lungs). This study was concerned with an accumulation of paraquat in lungs and kidneys, as a result of inhalation. This study can, therefore, be also classified as Core-Minimum data in the category of SPECIAL TESTING (163.85-1).

No reference was made to this study in Mr. Taylor's letters.

Toxicology Branch responds to Chevron's general and specific comments as follows.

General Comments:

For our purpose, the Key point of these comments is the statement on page 4 that "..... 0.1 ug/l is a no-effect level for paraquat exposure in the lung and ..... 0.01 ug/l is an overall no-effect level for all parameters studied." Our records are in agreement with Chevron's statement which is based on studies A and B. However, we do not list no-effect levels for specific organs in our evaluation and summaries of toxicological data. In this case, a comment is made in the evaluation of study A that changes in lung morphology were observed at the exposure level of 0.5 ug paraquat ion/l. It is also stated in the "oneliner" (summary of toxicology data) for paraquat that no pathological changes in rat lungs occurred at the exposure level of 0.1 ug paraquat ion/l.

Specific Comments:

1. Studies A and B:

Both studies were classified as supplementary (each study was evaluated by a different toxicologist) and Chevron requested that this classification be upgraded for the following reasons:

a. Hematology, clinical analyses, organ weighings and gross and microscopic examination of non-respiratory tissues were not conducted since the work was primarily concerned with the effect of paraquat aerosols on the respiratory tract.

b. Study B was a repetition of study A at the two lower exposure levels (0.01 and 0.1 ug paraquat ion/l) and should be evaluated in conjunction with study A and not considered as an independent study. The primary purpose of study B was to determine if the reduced body weight gains, observed at these levels in study A, were repeatable.

c. Because body weight changes were not observed in study B, it was unnecessary to repeat histopathology (on the respiratory tract) which was already performed in study A. see p4

Studies A and B were conducted separately, were received by Toxicology Branch separately, and were, therefore, evaluated separately. However, they were always considered together in matters concerning inhalation toxicity of paraquat. These studies were classified as supplementary because, considered individually or together, they are incomplete as subchronic inhalation studies. They are concerned primarily with the effects of paraquat on the respiratory tract and ignore parameters which must be tested in order to evaluate the effects of repeated inhalation exposures on the overall health of animals. The following parameters should also have been tested in a complete subchronic inhalation study: hematology, clinical analyses, organ weighings, and gross and microscopic examination of non-respiratory tissues.

2. Study C:

Toxicology Branch appreciates Chevron's comments regarding paraquat accumulation in the rat lungs at the 0.01 and 0.5 ug/l exposure levels. According to Chevron, this information was reported in study E (dated 8/22/80 and received by EPA on 12/9/80). Toxicology Branch completed the evaluation of study C on 7/8/80 and, therefore, had no access to this information at that time.

3. Study D:

Toxicology Branch appreciates the clarification of the objectives of this study. We accept Chevron's explanation regarding the use of ^{3}H-paraquat in preferance to ^{14}C paraquat.

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